(12) PATENT ABRIDGMENT (11) Document No. AU 36636/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 615553

(54) Title
AQUEOUS DIALYSIS AND RINSING SOLUTION FOR INTRAPERITONEAL ADMINISTRATION

International Patent Classification(s)
(51)[4] **A61K 031/195**

(21) Application No. : **36636/89** (22) Application Date : **20.06.89**

(30) Priority Data

(31) Number	(32) Date	(33) Country
3821043	**22.06.88**	**DE FEDERAL REPUBLIC OF GERMANY**

(43) Publication Date : **04.01.90**

(44) Publication Date of Accepted Application : **03.10.91**

(71) Applicant(s)
FRESENIUS AG

(72) Inventor(s)
VOLKER BARTZ; VOLKER STEUDLE

(74) Attorney or Agent
SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001

(56) Prior Art Documents
EP 218900

(57) Claim

1. Aqueous dialysis and rinsing solution for intraperitoneal administration containing electrolytes in physiological amounts, an amino acid mixture as osmotically active substance and possibly further additives, characterized in that the amino acid mixture contains the following amino acids in the following relative amounts expressed in parts by weight:

L-histidine	4 to 6 parts by wt.
L-isoleucine	6 to 9 parts by wt.
L-leucine	9 to 13.5 parts by wt.
L-methionine	9 to 12 parts by wt.
L-valine	13.5 to 20.5 parts by wt.
L-lysine hydrochloride	6.5 to 10 parts by wt.
L-phenylalanine	6 to 9.5 parts by wt.
L-threonine	6.5 to 10 parts by wt.
L-thyrosine	7.5 to 12 parts by wt.
L-taurine	2 to 8 parts by wt.
L-tryptophane	1 to 5 parts by wt.

6915553
S & F Ref: 98937

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name and Address of Applicant: Fresenius AG
Gluckensteinweg 5
6380 Bad Homburg v.d.H.
FEDERAL REPUBLIC OF GERMANY

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

Aqueous Dialysis and Rinsing Solution for Intraperitoneal Administration

The following statement is a full description of this invention, including the best method of performing it known to me/us

Abstract

Dialysis and rinsing solutions for intraperitoneal administration with usual electrolyte composition in physiological amounts and an amino acid mixture as osmotically active substance and possibly additionally organic acids or salts thereof and possibly further additives.

Description

The subject of the invention is aqueous dialysis and rinsing solutions for intraperitoneal administration containing electrolytes in physiological amounts, an amino acid mixture as osmotically acting substance and possibly further additives.

With patients with acute or chronic kidney deficiency the restricted kidney function must be compensated by alternative methods. Such alternative methods are hemodialysis and peritoneal dialysis. In hemodialysis the blood of the patient is purified extracorporeally with the aid of an artificial semipermeable membrane. In peritoneal dialysis the peritoneum serves as semipermeable membrane. The dialysis solution is introduced via a catheter into the peritoneal cavity. After a certain equilibration time, i.e. after concentration-dependent exchange from substances of the dialysis with the blood, the "spent" dialysis solution is then removed from the peritoneal cavity and replaced by a new dialysis solution. Peritoneal dialysis, for example continuous ambulant peritoneal dialysis (CAPD) or intermittent peritoneal dialysis, is becoming of increasing significance. Whereas the major part of the symptoms due to uremia can be managed very well with a long-term peritoneal dialysis, a number of metabolic defects exist which can be brought into connection with the osmotically active substance used or the buffer of the dialysate.

The essential task of a dialysis solution for kidney-deficient patients resides on the one hand in taking up excess water and substances usually eliminated with the urine and on the other hand in supplying substances which for metabolic reasons occur in insufficient concentration in the organism (electrolyte balance). In addition, with a peritoneal dialysis

solution a positive nutritive effect should be achieved for the patient, this being of significance in particular in view of the fact that the CAPD patient passes about 5 to 12 g protein and a few g amino acids into the dialysate daily.

Hitherto, glucose has been the most widely used osmotically active substance. Thus, all commercially available peritoneal dialysis solutions contain glucose as osmotically active substance to ensure a corresponding ultrafiltration. However, glucose has some disadvantages. CAPD patients absorb 150 to 300 g glucose from the dialysate daily. This amount corresponds approximately to a third of the daily calorie requirement and contributes to obesity. In particular in the case of diabetic patients hyperglycemia with increased insulin requirement has been described. This is encountered particularly with intermittent peritoneal dialysis. Hyperglycemia leads furthermore to hyperlipemia which can be the cause of atherosclerotic changes. Glucose is rapidly absorbed from the peritoneal cavity and as a result the osmotic gradient between peritoneal dialysis solution and plasma is reduced. This in turn is associated with a drop in the ultrafiltration. A further disadvantage of glucose is that it represents an excellent substrate for a great number of microorganisms and therefore the formation of microbial peritonitis is promoted.

To eliminate these disadvantages and problems involved with the use of glucose as osmotically active substance in dialysis solutions numerous investigations have been made with a view to finding alternative osmotically active substances. Thus, it was already proposed a long time ago to use amino acid solutions instead of glucose as osmotically active substances (cf. Lancet, Vol. 2, 1968, page 812).

According to PCT patent application WO 82/03773 a dialysis solution is proposed which contains an aqueous solution of physiological salts in concentration adequate for osmotic compatibility with the blood, a mixture of physiological amino acids and insulin in an amount sufficient to permit substantial assimilation of the amino acids for the patient. As example of a suitable amino acid mixture the PCT patent application gives the commercial prcduct Travesol, which can be contained in the dialysis solution in amounts of 1 to 4 g per 1. Preferably, the dialysis solutions according to this patent application also contain glucose in amounts of 0.5 to 4 g per 1. The addition of insulin tc the dialysis solution is intended to facilitate both the metabolization of the glucose and of the amino acids as well as the assimilation of the amino acids into the cells.

Admittedly, these dialysis solutions reduce or avoid the problems of hyperglycemia but it is not possible with these known amino-acid-containing dialysis solutions to achieve sufficient nutritive effect in the case of kidney-deficient patients.

There is therefore still a considerable need for osmotically active dialysis solutions which can be administered over longer periods of time to patients without complications due to osmotic phenomena or microbial complications occurring, and which ensure an adequate removal of water and substances normally eliminated with the urine, a correction of the electrolyte balance and an active nutritive effect in patients suffering from kidney deficiency.

The problem underlying the invention is therefore to provide osmotically active dialysis and rinsing or washing solutions which can be administered for a relatively long period of time to patients intraperitoneally without complications due to osmotic phenomena occurring, the microbial

and peritoneal dialysis complications occurring in hitherto known dialysis and rinsing solutions being avoided, an adequate withdrawal of water and substances normally eliminated in the urine being ensured as well as a correction of the electrolyte balance, and an effective nutritive contribution being made for the patient by the dialysis solution.

According to the invention this problem is solved by a dialysis or rinsing solution which as osmotically active substance comprises an amino acid mixture containing the following amino acids in the following relative amounts expressed in parts by weight:

L-histidine	4 to 6 parts by wt.
L-isoleucine	6 to 9 parts by wt.
L-leucine	9 to 13.5 parts by wt.
L-methionine	9 to 12 parts by wt.
L-valine	13.5 to 20.5 parts by wt.
L-lysine hydrochloride	6.5 to 10 parts by wt.
L-phenylalanine	6 to 9.5 parts by wt.
L-threonine	6.5 to 10 parts by wt.
L-tyrosine	7.5 to 12 parts by wt.
L-taurine	2 to 8 parts by wt.
L-tryptophane	1 to 5 parts by wt.

Preferably, the amino acid mixture according to the invention comprises the following amino acids in the following relative amounts expressed in parts by weight:

L-histidine	4.5 to 5 parts by wt.
L-isoleucine	6 to 6.5 parts by wt.
L-leucine	9 to 10 parts by wt.
L-methionine	9 to 10 parts by wt.
L-valine	13.5 to 15 parts by wt.
L-lysine hydrochloride	6.5 to 8 parts by wt.
L-phenylalanine	6 to 6.8 parts by wt.

L-threonine	6.5 to 7	parts by wt.
L-tyrosine	7.5 to 8.5	parts by wt.
L-taurine	4.5 to 6	parts by wt.
L-tryptophane	2 to 3	parts by wt.

In particular, an amino acid mixture is preferred which contains the amino acids in the following relative amounts:

L-histidine	4.9	parts by wt.
L-isoleucine	6.0	parts by wt.
L-leucine	9.0	parts by wt.
L-methionine	9.0	parts by wt.
L-valine	13.5	parts by wt.
L-lysine hydrochloride	6.5	parts by wt.
L-phenylalanine	6.0	parts by wt.
L-threonine	6.5	parts by wt.
L-tyrosine	7.5	parts by wt.
L-taurine	4.9	parts by wt.
L-tryptophane	2.5	parts by wt.

In the amino acid mixtures used according to the invention it is essential that specific ratios of isoleucine : leucine : valine are maintained. Thus, this ratio should be such that isoleucine < leucine < valine. Preferably, the ratio isoleucine : leucine : valine should be 1 : 1.5 : 2.15 to 2.25 and is in particular 1 : 1.5 : 2.25.

In the same manner the ratio of tyrosine : phenylalanine should be > 1. Preferably, it is 1.05 to 1.30 : 1 and in particular 1.25 : 1.

The amino acid mixture used according to the invention is employed in the dialysis and rinsing solutions according to the invention in an amount of 2.0 to 50.0 g amino acid mixture per 1. Preferably, the dialysis and rinsing solutions according to the invention contain 7.5 to 20 g amino acids

per 1 and in particular 7.5 to 12.5 g amino acid mixture/1, for example 10 g amino acid mixture per 1.

According to the invention it has been surprisingly found that when using the amino acid mixture set forth above it is possible when treating kidney-deficient patients to make an effective nutritive contribution. The composition of the amino acid according to the invention is adapted to the needs of the kidney-deficient patient. The basis of the composition of the amino acid mixture according to the invention is not the plasma amino acid pattern but the amino acid pattern of intracellular relevant amino acid pools (muscles).

According to a preferred embodiment the dialysis and rinsing solutions according to the invention contain one or more carboxylic acids in the form of their salts, for example the sodium, potassium or calcium salts. Examples of suitable salts are the succinate, fumarate, malate, oxalacetate and the like. Malate is preferably used.

These acids and their salts are present in the solutions according to the invention in amounts of 2 to 12 g/1, preferably in an amount of 6.53 g/1.

Examples of electrolyte additives for the dialysis and rinsing solutions according to the invention are electrolytes containing sodium, potassium, calcium or magnesium ions. According to the invention the electrolyte salts may be present in known manner in the form of the acetate, lactate, chloride and/or bicarbonate. The ion concentrations in the dialysis and rinsing solutions according to the invention are preferably 125 to 150, in particular 132 to 140 mmol/1 Na^+; 0 to 8, in particular 0 to 4 mmol/1 K^+; 0 to 3, in particular 0.5 to 2 mmol/1 Ca^{++}; 0 to 2.5, in particular

0.3 to 1 mmol/l Mg^{++}; 10 to 60, in particular 30 to 50 mmol/l ions, selected from the group of the lactate, acetate and bicarbonate ions and the remainder Cl^-.

The dialysis and rinsing solutions according to the invention may contain other suitable physiologically neutral additives which are added in the form of solutions or emulsions to the solutions according to the invention. Examples of such additives are vitamins, water-soluble carbohydrates, hormones influencing the protein metabolism, fatty acids and/or fats, glycerin, glycerides and possibly suitable emulsifiers. These additives may be employed according to the invention in amounts as generally usual in pharmacology.

Examples of vitamins are water-soluble and fat-soluble vitamins such as the vitamins A, D, E, B_1, B_2, B_6 and B_{12}, vitamin K, vitamin C, niacin, pantothenic acid, biotin and folic acid. Preferably used are the vitamins of the vitamin B group, for example vitamin B_1, B_2 and B_6, pantothenic acid, niacin, biotin and vitamin C. The vitamins may be used individually or in a mixture. The dialysis and rinsing solutions according to the invention generally contain the vitamins in an amount of 10 to 500 mg/l, preferably in an amount of 100 to 200 mg/l, for example in an amount of 150 mg/l.

Examples of water-soluble carbohydrates are monosaccharides such as glucose, fructose, galactose and sugar alcohols, such as sorbite or xylite. The carbohydrates may be used individually or in a mixture. Preferably glucose is employed. The solutions according to the invention may contain the carbohydrates in an amount of 0 to 10% by weight, preferably in an amount of 0 to 5% by weight, for example 1% by weight.

Examples of hormones influencing the protein metabolism are androstanolone or nortestosterone. The hormones may be

employed individually or in a mixture. In the mixtures according to the invention these hormones can be contained generally in a pharmacologically effective amount.

Examples of suitable fatty acids are fatty acids having 5 to 24 carbon atoms. Examples of suitable fats are unsaturated fats such as soybean oil, cottonseed oil or fish oils.

According to the invention generally the fats are employed in the form of emulsions using a suitable emulsifier, such as lecithins, such as soy lecithin or purified lecithin from chicken egg. The fats and/or fatty acids as well as glycerin or glycerides may be used in the solutions according to the invention in amounts of 0 to 300 g/l, preferably 0 to 200 g/l.

The pH value of the solutions according to the invention lies in the acid range, preferably in the range from 5.5 to 6.5, and is for example 5.6.

The osmotic pressure of the dialysis and rinsing solutions according to the invention is suitably 300 to 700 mosm/l, preferably 320 to 550 mosm/l and in particular 350 to 500 mosm/l.

The preparation of the dialysis and rinsing solutions according to the invention may be carried out by the methods known for preparing dialysis and rinsing solutions. For example, the preparation may be carried out in the manner described in PCT patent application WO 82/03773. For example, in the case of the additional use of carbohydrates the sterilization can take place in a double-chamber bag, the carbohydrate solution (e.g. glucose solution) being disposed in one chamber and the amino acid solution with the further constituents being disposed in the other chamber, and after sterilization whilst maintaining sterile conditions a

connection of the chambers with each other can be established and the two separately sterilized solutions are mixed.

The dialysis and rinsing solutions according to the invention are excellently suited for peritoneal administration. They are extremely effective (adequate withdrawal of water and substances normally eliminated in the urine and suitable correction of the electrolyte balance) and can be administered over longer periods of time without the microbial and peritoneal-dialysis complications hitherto encountered with dialysis solutions occurring. The dialysis and rinsing solutions according to the invention avoid hyperglycemia, obesity, loss of appetite, and hyperlipemia, in particular in diabetic patients. With the solutions according to the invention the ultrafiltration maximum is reached considerably earlier than with the known dialysis solutions containing glucose as osmotically active substance, making them particularly suitable for rapid dehydration. Moreover, with the solutions according to the invention an effective nutritive contribution is ensured for patients with kidney deficiency. The daily amino acid loss is corrected by these agents and the protein synthesis thereby stimulated, thus ensuring a general improvement of patient status.

The following examples serve for further explanation of the present invention:

Example 1:

a) In one litre of water of injection quality a solution of the following amino acids is prepared:

L-histidine	4.9 g/l
L-isoleucine	6.0 g/l
L-leucine	9.0 g/l
L-methionine	9.0 g/l
L-valine	13.5 g/l
L-lysine hydrochloride	6.5 g/l

L-phenylalanine	6.0 g/l
L-threonine	6.5 g/l
L-tyrosine	7.5 g/l
L-taurine	4.9 g/l
L-tryptophane	2.5 g/l.

This solution is diluted to a final concentration of 10 g/l amino acids.

b) Using the solution described above a dialysis and rinsing solution according to the invention is prepared. This solution contains in one l water of injection quality the following constituents:

Amino acid mixture according to a)	10 g/l
L-maleic acid	6.53 g/l
NaCl	5.785 g/l
$CaCl_2 x 2H_2O$	0.2573 g/l
$MgCl_2 x 6H_2O$	0.1017 g/l
Na-lactate, 50% solution	10.76 g/l (48 mmol/l)
Glucose	10.0 g/l
Pyridoxine HCL	40.0 mg/l
Riboflavine-5-phosphate	2.5 mg/l
Nicotinamide	60 mg/l
Thiamine	10 mg/l

The theoretical osmotic pressure of the solution thus made was 500 mosm/l; pH value: 5.6.

Example 2:

Example 1 was repeated with the exception that the amino acid mixture according to a) of Example 1 was used in an amount of 7.5 g/l.

~~Claims~~

The claims defining the invention are as follows:

1. Aqueous dialysis and rinsing solution for intraperitoneal administration containing electrolytes in physiological amounts, an amino acid mixture as osmotically active substance and possibly further additives, characterized in that the amino acid mixture contains the following amino acids in the following relative amounts expressed in parts by weight:

L-histidine	4 to 6	parts by wt.
L-isoleucine	6 to 9	parts by wt.
L-leucine	9 to 13.5	parts by wt.
L-methionine	9 to 12	parts by wt.
L-valine	13.5 to 20.5	parts by wt.
L-lysine hydrochloride	6.5 to 10	parts by wt.
L-phenylalanine	6 to 9.5	parts by wt.
L-threonine	6.5 to 10	parts by wt.
L-thyrosine	7.5 to 12	parts by wt.
L-taurine	2 to 8	parts by wt.
L-tryptophane	1 to 5	parts by wt.

2. Solution according to claim 1, characterized in that the amino acid mixture comprises the following composition expressed in parts by weight:

L-histidine	4.5 to 5	parts by wt.
L-isoleucine	6 to 6.5	parts by wt.
L-leucine	9 to 10	parts by wt.
L-methionine	9 to 10	parts by wt.
L-valine	13.5 to 15	parts by wt.
L-lysine hydrochloride	6.5 to 8	parts by wt.
L-phenylalanine	6 to 6.8	parts by wt.
L-threonine	6.5 to 7	parts by wt.

L-tyrosine	7.5 to 8.5 parts by wt.
L-taurine	4.5 to 6 parts by wt.
L-tryptophane	2 to 3 parts by wt.

3. Solution according to claim 1 or 2, characterized in that the ratio of the amino acids isoleucine : leucine : valine is 1 : 1.5 : 2.25.

4. Solution according to claims 1 to 3, characterized in that the ratio of the amino acids tyrosine : phenylalanine is 1.25 : 1.

5. Solution according to claims 1 to 4, characterized in that it contains the amino acid mixture in an amount corresponding to 2 to 50 g amino acids/l.

6. Solution according to claim 5, characterized in that it contains the amino acids in an amount corresponding to 7.5 to 20 g amino acids/l.

7. Solution according to claim 6, characterized in that it contains the amino acids in an amount corresponding to 7.5 to 12.5 g amino acids/l.

8. Solution according to claims 1 to 7, characterized in that it has an osmotic pressure in the range from 300 to 700 mosm/l.

9. Solution according to claim 8, characterized in that the osmotic pressure is 320 to 550 mosm/l.

10. Solution according to claims 1 to 9, characterized in that the pH value lies in the acid range.

11. An aqueous dialysis and rinsing solution for intraperitoneal administration containing electrolytes in physiological amounts, an amino acid mixture as osmotically active substance, substantially as herein described with reference to Example 1 or 2.

DATED this SIXTEENTH day of JUNE 1989

Fresenius AG

Patent Attorneys for the Applicant

SPRUSON & FERGUSON